

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
12 May 2005 (12.05.2005)

PCT

(10) International Publication Number
WO 2005/042009 A1

(51) International Patent Classification⁷: **A61K 38/19**,
39/395, A61P 37/00

(21) International Application Number:
PCT/US2004/034514

(22) International Filing Date: 20 October 2004 (20.10.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/512,880 20 October 2003 (20.10.2003) US

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: THERAPEUTIC REGIMENS FOR BAFF ANTAGONISTS

(57) Abstract: Therapeutic regimens for administration of BAFF antagonists for treatment of immunologic and related disorders are described. Regimens involve a short-term BAFF antagonist administration course followed by an extended no-treatment period prior the round of administration.

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THERAPEUTIC REGIMENS FOR BAFF ANTAGONISTS

[0001] This application claims priority to U. S. Provisional Application No. 60/512,880, filed October 20, 2003, which is hereby incorporated by reference.

Field of the Invention

[0002] The present invention generally relates to therapeutic regimens used in treating immunologic and related disorders. More specifically, the invention relates to methods of treating autoimmune disorders utilizing antagonists of BAFF (B cell activating factor belonging to the TNF family).

Background of the Invention

[0003] B cells play a central role in acquired immunity. These cells possess the unique ability to mount a rapid and directed antibody (Ab) response against foreign antigens (Ag), and to act as Ag presenting cells. To maintain B cell homeostasis and a self-tolerant state, it is necessary to generate a continuous pool of B cell precursors that will mature and migrate to peripheral organs, as well as maintain a process of negative selection to eliminate autoreactive B cells. Dysregulation in the B cell developmental process could lead to a block in B cell development, and thus immune deficiency, or conversely, to an escape and expansion of self-reactive B cells leading to autoimmunity.

[0004] Generation of high affinity, somatically hypermutated autoantibodies is one of the hallmarks of autoimmune conditions. The

autoantibodies can cause severe tissue damage (e.g., as in lupus nephritis) or loss of blood components (e.g., as in immune thrombocytopenia purpura). The prevailing treatment strategies for autoimmune disorders employ global immunosuppressants that have harmful side effects with long-term use.

[0005] Recent discovery of the B cell survival and maturation factor BAFF (also known as TALL-1, THANK, BLyS, zTNF4, and TNFSF13B) provided a unique opportunity for developing targeted intervention strategies for autoreactive B cell function. Elucidation of the role of BAFF in acquired immunity has been rapid since its first description as a B cell growth factor. BAFF (Accession No. AAD25356) is described in, e.g., Schneider et al (1999) J. Exp. Med., 189:1697-1710; PCT Publication WO 99/12964 and United States Patent Application No. 09/911,777. Studies have indicated that higher than normal levels of BAFF may contribute to the pathogenesis of autoimmune diseases, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis. For a review, see, e.g., Mackay et al. (2002) Nature Reviews: Immunology, 2:465-475; Kalled et al. (2003) Expert Opin. Ther. Targets, 7(1):115-23.

[0006] BAFF has been implicated in costimulation of B cells (Moore et al. (1999) Science, 285:260-263; Schneider et al. (1999) J. Exp. Med., 189:1747-1756; Mukhopadhyay et al. (1999) J. Biol. Chem., 274:15978-15981); increased B cell proliferation (Moore et al. (1999) Science, 285:260-263); and increased survival of normally deleted B cells (Khare et al. (2000) Proc. Natl. Acad. Sci., 97:3370-3375; Gross et al. (2000) Nature, 404:995-999; Mackay et al. (1999) J. Exp. Med., 190:1697-1710). Three

cognate receptors for BAFF have been identified: (1) B cell maturation antigen (BCMA; Accession No. S43486; Gross et al. (2000) *Nature*, 404:995-999; PCT Publication WO 01/12812; United States Patent Application No. 10/077,137); transmembrane activator and cyclophilin ligand interactor (TACI; Accession No. AAP57629; Gross et al., *supra*); and most recently, BAFFR (also called BR3; Accession No. AF373846; Thompson et al. (2001) *Science*, 293:2108-2111). BAFFR is the only one of the three receptors that is specific for BAFF (Thompson et al., *supra*). BCMA and TACI bind not only to BAFF but also to another TNF family ligand, APRIL (Yu et al. (2000) *Nat. Immunol.*, 1:252-256; Wu et al. (2000) *J. Biol. Chem.*, 275:35478-35485; Rennert et al. (2000) *J. Exp. Med.*, 192:1677-1684; PCT Publication WO 01/24811; United States Patent Application No. 10/115,192).

[0007] While BAFF has been unambiguously identified as a factor required for B cell survival and maturation, the role of APRIL in B cell homeostasis remains less well understood. APRIL was originally found to stimulate growth of tumor cells in vitro and in vivo (Hahne et al. (1998) *J. Exp. Med.*, 188:1185-1190). Recent reports demonstrated that APRIL may act also as a costimulator of primary B and T cells in vitro and stimulate IgM production by peripheral blood B cells in vitro (Yu et al. (2000) *Nat. Immunol.*, 1:252-256; Marsters et al. (2000) *Curr. Biol.*, 10:785-788). In vivo administration of APRIL, like BAFF, results in splenomegaly due to expansion of the B cell population and an increase in the percentage of activated T cells (Yu et al. (2000) *Nat. Immunol.*, 1:252-256), suggesting that APRIL may be involved in lymphoid homeostasis. Based on data generated using APRIL-

transgenic mice, APRIL appears to play a role in T cell-independent type 2 (TI-2) humoral responses (Stein et al. (2002) *J. Clin. Invest.*, 109(12): 1587-1598). Further, data generated using A/WySnJ mice demonstrate that APRIL is not required for B cell development and function (Thompson et al., *supra*).

[0008] Soluble forms of BAFF receptors have been made by fusing their extracellular domains to the Fc portion of immunoglobulin. Treatment of normal mice with such a soluble form of TACI or BCMA (TACI-Fc or BCMA-Fc) leads to reduced B cell numbers and a lack of humoral response (Shu et al. (1999) *J. Leukoc. Biol.*, 65:680-683; Yan et al. (2000) *Nat. Immunol.*, 1:37-41; Xia et al. (2000) *J. Exp. Med.*, 192:137-143; Wang et al. (2001) *Nat. Immunol.*, 2:632-637; Yu et al. (2000) *Nat. Immunol.*, 1:252-256). For example, in a mouse model for rheumatoid arthritis, an autoimmune disease that involves both B and T cell components, TACI-Fc substantially inhibits inflammation and slows disease progression (Wang et al. (2001) *Nat. Immunol.*, 2(7):632-637). These effects are thought to be attributed to BAFF sequestration because BAFF-deficient mice have a phenotype similar to that of TACI-Fc- or BCMA-Fc-treated mice (almost complete loss of mature B cells and a severely compromised humoral response) (Schiemann et al. (2001) *Science*, 293:2111-2114; Gross et al. (2001) *Immunity*, 15:289-302). Although a five-week treatment of NZBWF1 with TACI-Ig lead to a reduction in SLE symptoms at 12 weeks after the treatment, no reduction in autoantibodies was observed, indicating that a longer course of treatment may be necessary (Gross et al. (2000) *Nature*, 404(6781):995-999).

[0009] Recently, BAFF-specific agents, including BAFFR-Fc and BAFF antibodies, have been developed for treatment of autoimmune and other disorders (see, e.g., United States Patent Application Nos. 09/911,777; 10/380,703; 10/045,574; and 60/458,707); Kalled et al. (2003) Expert Opin. Ther. Targets, 7(1):115-23). Once the administration of a BAFF-specific agent has ceased and the agent is eliminated from the bloodstream, B cell reconstitution to pre-treatment levels, including recovery of pathogenic B cells, is expected to occur within about 8 weeks (see, e.g., Porpiglia et al. (2003) Clin. Immunol., 107:90-97; Berardi et al. (1997) Blood, 89:3554-3564; Hiramatsu et al. (2003) Blood, 102:873-880). As a result, frequent administration of these drugs, at intervals of less than 8 weeks, may be necessary to maintain therapeutic benefits.

[0010] Therefore, new therapeutic strategies are still needed for the treatment of immune and related disorders.

SUMMARY OF THE INVENTION

[0011] The present invention results from the realization that effective treatment of immunologic disorders can be accomplished by a short-term administration of a therapeutically effective amount of a BAFF antagonist, thereafter, temporarily discontinuing the administration of the antagonist for an extended period prior to the next round of the administration.

[0012] The invention is based, in part, on the surprising finding that a short-term 4-week administration of BAFFR-Fc to nephritic SNF1 mice with mild-to-moderate SLE results in a long-term clinical benefit (at least 6 months). Although B cell recovery does take place following administration of

BAFFR-Fc, the newly emerging B cells are substantially non-pathogenic. The invention is further based, on the discovery and demonstration that the clinical effect of the short-term BAFFR-Fc administration in the SNF1 mice is significantly more pronounced and long-lasting as compared to the clinical effect observed upon administration of TACI-Fc in the same model.

[0013] The present invention provides methods for treating immunologic and related disorders in mammals, in particular autoimmune disorders, and includes (but is not limited to) methods for inhibiting autoantibody production, and/or inhibiting the generation of pathogenic B cell population in a mammal. The invention further provides methods for treating renal fibrosis and/or improving renal function, such as, e.g., pressure filtration, selective reabsorption, tubular secretion, and systemic blood pressure regulation. The invention yet further provides methods for decreasing cardiac inflammation. Methods of administration and compositions used in the methods of the inventions are also provided.

[0014] In certain embodiments, the method of treating a patient having an immunologic disorder, comprises:

(a) administering to the patient a therapeutically effective amount of a BAFF (B cell activating factor belonging to the TNF family) antagonist at least once or at one or more intervals of less than N weeks;

(b) temporarily discontinuing the administration of step (a) for N weeks or longer; and

(c) repeating steps (a) and (b) at least once;

wherein N is 8, 9, 10, 11, or 12.

[0015] In some embodiments, the BAFF antagonist is a soluble BAFF receptor (e.g., BAFFR, BCMA, or TACI), an anti-BAFF antibody, or an anti-BAFF receptor antibody. In certain embodiments, the BAFF antagonist is BAFF-specific such as, for example, soluble BAFFR.

[0016] Additional aspects of the invention will be set forth in part in the following description, and in part will be understood from the description or may be learned by practice of the invention.

BRIEF DESCRIPTION OF THE SEQUENCES

[0017] SEQ ID NO:1 is an amino acid sequence of human BAFFR (GenBank™ Accession No. AF373846). Special features noted in the Sequence Listing for this sequence: residue 1 - none or any amino acid; residue 2 - methionine, none, or any amino acid; residue 21 - valine (wild type), asparagine, or another amino acid; residue 28 - lysine (wild type), proline, or another amino acid; residue 47 - none, any amino acid, or alanine.

[0018] SEQ ID NO:3 is an amino acid sequence of human BAFFR-Fc fusion protein, which includes a signal sequence (amino acids 1-22) and a human IgG1 Fc portion (amino acids 95-321). Special features noted in the Sequence Listing for this sequence: residue 41 - valine (wild type), asparagine, or another amino acid; residue 48 - lysine (wild type), proline, or another amino acid; residue 67 - none, any amino acid, or alanine.

[0019] SEQ ID NO:2 is an amino acid sequence of murine BAFFR (GenBank™ Accession No. Q96RJ3).

[0020] SEQ ID NO:4 is an amino acid sequence of murine BAFFR-Fc fusion protein, which includes a signal sequence (amino acids 1-22) and a murine IgG1 Fc portion (amino acids 88-316).

[0021] SEQ ID NO:5 is an amino acid sequence of a BAFF-binding peptide derived from BAFFR.

[0022] SEQ ID NO:6 is an amino acid sequence of a minimal deletion in Δ BAFFR described in United States Patent Application No. 60/458,707.

BRIEF DESCRIPTION OF THE FIGURES

[0023] Figures 1A-1D demonstrate that a short-term BAFFR-Fc treatment inhibits renal lymphocyte infiltration in the kidneys of SNF1 mice as assessed by immunohistochemistry on paraffin-embedded kidney sections using biotin-anti-B220 mAb for B cells and anti-CD3 for T cells (50x magnification). Figs. 1A and 1B show representative kidney sections from untreated mice of 9 and 50 weeks of age, respectively. Two groups of mice were administered either 200 μ g of murine BAFFR-Fc or 200 μ g of mIgG1, two times per week for four consecutive weeks starting at 23 weeks of age, and sacrificed at the age of 50 or 51 weeks, respectively. Figs. 1C and 1D show representative kidney sections from BAFFR-Fc- and mIgG1-treated mice, respectively.

[0024] Figures 2A-2D demonstrate that a short-term BAFFR-Fc treatment inhibits lymphadenopathy in SNF1 mice as assessed by immunohistochemistry on paraffin-embedded mesenteric lymph node (MLN) sections using biotin-anti-B220 mAb for B cells and anti-CD3 for T cells (50x

magnification). Figs. 2A and 2B show representative MLN sections from untreated mice of 9 and 50 weeks of age, respectively. Two groups of mice were administered either 200 µg of murine BAFFR-Fc or 200 µg of mIgG1, two times per week for four consecutive weeks starting at 23 weeks of age, and sacrificed at the age of 50 or 51 weeks, respectively. Figs. 2C and 2D show representative MLN sections from BAFFR-Fc- and mIgG1-treated mice, respectively.

DETAILED DESCRIPTION OF THE INVENTION

[0025] In order that the present invention may be more readily understood, certain terms are first defined. Additional definitions are set forth throughout the detailed description.

[0026] The term “antibody,” as used herein, refers to an immunoglobulin or a part thereof, and encompasses any polypeptide comprising an antigen-binding site regardless of the source, method of production, and other characteristics. The term includes but is not limited to polyclonal, monoclonal, monospecific, polyspecific, non-specific, humanized, single-chain, chimeric, synthetic, recombinant, hybrid, mutated, and CDR-grafted antibodies. The term “**antigen-binding domain**” refers to the part of an antibody molecule that comprises the area specifically binding to or complementary to a part or all of an antigen. Where an antigen is large, an antibody may only bind to a particular part of the antigen. The “epitope,” or “antigenic determinant” is a portion of an antigen molecule that is responsible for specific interactions with the antigen-binding domain of an antibody. An antigen-binding domain may be provided by one or more antibody variable

domains (e.g., a so-called Fd antibody fragment consisting of a V_H domain). An antigen-binding domain comprises an antibody light chain variable region (V_L) and an antibody heavy chain variable region (V_H). The terms "**anti-BAFF antibody**" and "**antibody directed against BAFF**" refer to any antibody that specifically binds to at least one epitope of BAFF.

[0027] The term "BAFF" refers to B cell-activating factor, characterized by expression in immune cells and its role as a B cell survival factor. A summary of BAFF's characteristics is provided in Mackay et al. (2002) Nature Reviews: Immunology 2:465-475 and in Gavin et al. (2003) J. Biol. Chem., 278(40):38220-8.

[0028] As used herein, "BAFF antagonist" generally refers to any compound that directly downregulates the biological activity of BAFF. A molecule "directly downregulates" the biological activity of BAFF by interacting with a BAFF; BAFF gene, a BAFF transcript, or a BAFF receptor. A BAFF antagonist may, for example, bind to and neutralize the activity of BAFF; decrease BAFF expression levels; affect stability of BAFF; affect proteolytic cleavage of the membrane-bound form of BAFF into the soluble form; interfere with the binding of BAFF to one or more receptors; or it may interfere with intracellular signaling of a BAFF receptor. BAFF antagonists may be proteinaceous (e.g., antibodies, receptor fusion proteins, peptides) or non-proteinaceous molecules (e.g., small organic molecules (≤ 500 Da)). Methods for assessing neutralizing biological activity of BAFF antagonists are known in the art.

[0029] The term "BAFFR," unless otherwise stated, refers to a protein that comprises at least a portion of wild-type or mutant receptor for BAFF, other than BCMA or TACI, that is capable of binding to BAFF. It has been determined that the BAFF-binding domain of human BAFFR contains amino acids 27 to 32 of SEQ ID NO:1. BAFFR is further defined in PCT Publication WO 02/24909 and United States Patent Applications Nos. 10/380,703 and 60/458,707, and specifically includes, but is not limited to, human BAFFR (SEQ ID NO:1; Accession No. AAD25356; amino acid 47 of SEQ ID NO:1 is not present in some isoforms) and murine BAFFR (SEQ ID NO:3; Accession No. Q96RJ3). "BAFFR" also refers to naturally occurring variants, e.g., the splice variant containing an alanine at amino acid 47 of SEQ ID NO:1 corresponding to amino acid 67 of SEQ ID NO:2, as well as functional mutated forms of BAFFR, e.g., human BAFFR having mutations at least at amino acids 21 and 28 of SEQ ID NO:1 (e.g., V21N and L28P). The terms "BAFFR-Fc" and "BAFFR-Ig" refer to a fusion protein comprising BAFFR and antibody constant region sequences, such as, for example, an Fc portion.

[0030] The term "BAFF-specific antagonist" refers to a compound that: (1) has the ability to counteract the effect(s) of BAFF in vivo or in vitro, e.g., by competitive blockage of one or more BAFF receptors, and (2) under physiologic conditions preferentially forms a relatively stable complex with BAFF but not with other ligands of the TNF family, such as, e.g., APRIL. Typically, the binding is considered specific when the affinity constant K_a for BAFF is higher than 10^6 M^{-1} , preferably higher than 10^8 M^{-1} , while the

affinity for another TNF family ligand is lower than 10^6 M⁻¹, preferably lower than 10^5 M⁻¹. A skilled artisan recognizes that under certain conditions a low affinity but high avidity binding may also be specific even though K_a of the interaction may be relatively low. In some embodiments, affinity constant K_a of a BAFF-specific antagonist for at least one isoform of BAFF is preferably greater than 10^6 M⁻¹, 10^7 M⁻¹, 10^8 M⁻¹, 10^9 M⁻¹, 10^{10} M⁻¹, 10^{11} M⁻¹, or 10^{12} M⁻¹.

[0031] The phrase "substantially identical" means that a relevant amino acid sequence is at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99%, or 100% identical to a given sequence. By way of example, such sequences may be variants derived from various species, or they may be derived from the given sequence by truncation, deletion, amino acid substitution or addition. Percent identity between two amino acid sequences may be determined by standard alignment algorithms such as, for example, Basic Local Alignment Tool (BLAST) described in Altschul et al. (1990) J. Mol. Biol., 215:403-410, the algorithm of Needleman et al. (1970) J. Mol. Biol., 48:444-453, or the algorithm of Meyers et al. (1988) Comput. Appl. Biosci., 4:11-17. Such algorithms are incorporated into the BLASTN, BLASTP, and "BLAST 2 Sequences" programs (see www.ncbi.nlm.nih.gov/BLAST). When utilizing such programs, the default parameters can be used. For example, for nucleotide sequences the following settings can be used for "BLAST 2 Sequences": program BLASTN, reward for match 2, penalty for mismatch -2, open gap and extension gap penalties 5 and 2 respectively, gap x_dropoff 50, expect 10, word size 11, filter ON. For amino acid sequences the following

settings can be used for "BLAST 2 Sequences": program BLASTP, matrix BLOSUM62, open gap and extension gap penalties 11 and 1 respectively, gap x_dropoff 50, expect 10, word size 3, filter ON.

[0032] The term "immunologic disorder" refers to disorders and conditions in which an immune response is aberrant. The aberrant response can be due to (a) abnormal proliferation, maturation, survival, differentiation, or function of immune cells such as, for example, T or B cells. Example of immunologic disorders include, but are not limited to, rheumatoid arthritis (RA), asthma, psoriasis, multiple sclerosis (MS), inflammatory bowel disease (IBD), Crohn's disease, systemic lupus erythematosus (SLE), type I diabetes, Wegener's granulomatosis, transplant rejection, graft-versus-host disease (GVHD), hyperproliferative immune disorders, autoimmune diseases, B cell cancers, immunomodulation, antibody-mediated pathologies (e.g., ITCP, myasthenia gravis, and the like), and Sjogren's syndrome. The disorders that can be treated using the compositions and methods of the present invention include but are not limited to disorders described in PCT Publication WO 02/24909 and United States Patent Application Nos. 09/911,777; 10/380,703; 10/045,574; and 60/458,707.

[0033] The term "therapeutic" and cognates thereof, as used herein, refer to amelioration of clinical manifestations of a disorder, or production of a desired biological outcome. Examples of desirable outcomes include: reduced B cell hyperplasia; reduced autoantibody titer; reduced pathogenic B cell population; reduced cardiac inflammation; improving renal function (e.g., pressure filtration, selective reabsorption, tubular secretion, and systemic

blood pressure regulation), slowed progression renal fibrosis, reduced renal lymphocyte infiltration; reduced lymphadenopathy, etc. Outcomes can be determined using methods known in the art and/or as described herein.

[0034] The term "pathogenic B cell" refers to a B cell that produces autoantibody which contributes to disease pathology.

[0035] The invention is based, in part, on the surprising finding that a short-term 4-week administration of BAFFR-Fc to nephritic SNF1 mice with mild-to-moderate systemic lupus erythematosus (SLE) results in a long-term clinical benefit (at least 6 months). Given a short circulatory half-life of BAFFR-Fc in SNF1 mice (3.7 days), once BAFFR-Fc administration has ceased and BAFFR-Fc is eliminated from the bloodstream, B cell reconstitution is expected to occur within about 8 weeks. In experiments leading to the present invention, B cell recovery did take place following administration of BAFFR-Fc. However, the newly emerging B cells were found to be substantially non-pathogenic. The invention is further based, on the discovery and demonstration that the clinical effect of the short-term BAFFR-Fc administration in the SNF1 mice is significantly more pronounced and long-lasting as compared to TACI-Fc in the same model.

[0036] Methods of the inventions, compositions used therein, and other aspects of the invention are described in detail below.

[0037] Methods

[0038] The invention provides therapeutic regimens that involve a short-term BAFF antagonist administration course followed by an extended no-treatment period prior to the next round of administration.

[0039] In one aspect, the invention provides a therapeutic regimen for treating a patient having an immunologic or a related disorder. The regimen comprises:

(a) administering to the patient a therapeutically effective amount of a BAFF (B cell activating factor belonging to the TNF family) antagonist at least once or at one or more intervals of less than N weeks;

(b) temporarily discontinuing the administration of step (a) for N weeks or longer; and

(c) repeating steps (a) and (b) at least once;

wherein N is 8, 9, 10, 11, or 12.

[0040] In further embodiments, the administration of step (a) comprises an interval of 1, 2, 3, 4, 5, 6, or 7 weeks. In step (a), the BAFF antagonist may, for example, be administered 2, 3, 4, 5, 6, or 7 times a week, weekly, biweekly, every 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 weeks. In the administration period of step (a), the intervals between sequential administrations as well as dosages may vary. For example, in the administration period of step (a), the BAFF antagonist may be administered twice in the first week, withdrawn for three weeks, administered once, withdrawn for next 5 weeks, then administered daily for a week. In various embodiments, the administration is temporarily discontinued, as in step (b), for 8, 9, 10, 11, 12, 18, 24, 30, 36, 42, 48 weeks or a longer period which may be limited to 50, 80, 110, 140, 180, 210, 260, or 300 weeks.

[0041] In one aspect, the invention provides methods for treating immunologic and related disorders in mammals, in particular autoimmune

disorders, and includes (but is not limited to) methods for reducing autoantibody titer (e.g., anti-nuclear antibodies such as, for example, anti-ssDNA, anti-Sm, anti-RNP, and anti-Ro).

[0042] In another aspect, the invention further provides methods for treating renal fibrosis and/or improving renal function, such as, e.g., pressure filtration, selective reabsorption, tubular secretion, and systemic blood pressure regulation. In yet another aspect, the invention yet further provides methods for decreasing cardiac inflammation.

[0043] The invention further provides a method of reducing a pathogenic B cell population in a patient having an immune disorder. In certain embodiments, the pathogenic population of B cells is composed of B cells that are IgM-IgD+. B cell populations can be determined using, for example, antibodies to commonly used B cell markers such as, e.g., the B220 isoform of CD45 (Kincade et al. (1981) J. Immunol., 127: 2262-2268), or CD19 (see e.g., Krop et al. (1996) Eur. J. Immunol., 26:238-242) and respective isotype anti-immunoglobulin antibodies using methods known in the art and/or as described in the Examples.

[0044] The compositions of the invention may be administered in any manner that is medically acceptable. "Administration" is not limited to any particular delivery system and may include, without limitation, parenteral (including subcutaneous, intravenous, intramedullary, intraarticular, intramuscular, or intraperitoneal injection) rectal, topical, transdermal, or oral (for example, in capsules, suspensions, or tablets). Administration to an individual may occur in a single dose or in repeat administrations, and in any

of a variety of physiologically acceptable salt forms, and/or with an acceptable pharmaceutical carrier and/or additive as part of a pharmaceutical composition (described earlier). Physiologically acceptable salt forms and standard pharmaceutical formulation techniques and excipients are well known to persons skilled in the art (see, e.g., Physicians' Desk Reference (PDR) 2003, 57th ed., Medical Economics Company, 2002; and Remington: The Science and Practice of Pharmacy, eds. Gennado et al., 20th ed, Lippincott, Williams & Wilkins, 2000).

[0045] Administration of an antagonist to an individual may also be accomplished by means of gene therapy, wherein a nucleic acid sequence encoding the antagonist is administered to the patient in vivo or to cells in vitro, which are then introduced into a patient, and the antagonist (e.g., antisense RNA, soluble BAFF receptor) is produced by expression of the product encoded by the nucleic acid sequence.

[0046] In certain embodiments, the patient to be treated using the methods of the invention has mild, moderate, or severe disease. In various embodiments, patients are those having an immunologic disorder and/or are at increased risk for developing renal insufficiency. The treatment may be particularly useful in patients with proteinuria of over 1, 1.2, 1.5, 1.7, 2.0 g per a 24-hour period, and/or serum creatinine levels of 1.0, 1.5, 2.0, 2.5 mg/dl or higher. Other indications include creatinine clearance levels of lower than 97, 90, 80, 70, 60 (men) and 88, 80, 70, 60 (women) ml/min, blood urea of 20, 25, 30 mg/dl or higher, and/or those indicated by renal imaging (e.g., MRI, ultrasound), or renal biopsy. Yet other indications include above normal titer

of antinuclear antibodies in the serum (e.g., anti-ssDNA, anti-Sm, anti-RNP, and anti-Ro) or above normal peripheral blood B cell (e.g., CD19+) counts of over 700, 1000, 1250, 1500, 2000 cells/ μ l. Tests for assessing these parameters can be performed using methods known in the art, as described in the Examples, or in Jacobs et al. (eds.) (2002) Laboratory test handbook: Concise with disease index (2nd ed.) Husson, OH, Lexi-Comp.

[0047] The methods of the invention may be also used for treating patient having immunologic disorders where there is abnormal proliferation, maturation, survival, differentiation, or function of immune cells, such as, for example, B or T cells. The methods of the invention can be useful for treating pre-B or B cell leukemias, such as plasma cell leukemia, chronic or acute lymphocytic leukemia, myelomas (e.g., multiple myeloma, plasma cell myeloma, endothelial myeloma, and giant cell myeloma), and lymphoma (e.g., non-Hodgkin's lymphoma), Burkitt's lymphoma, non-Burkitt's lymphoma, follicular lymphoma, acute lymphoblastic leukemia, large cell lymphoma (e.g., immunoblastic lymphoma), marginal zone lymphoma, mantle cell lymphoma, small lymphocytic lymphoma, other B cell lymphomas, glomerulonephritis associated with diseases such as membranous nephropathy, IgA nephropathy (Berger's disease), IgM nephropathy, Goodpasture's disease, post-infectious glomerulonephritis, mesangioproliferative disease, chronic lymphoid leukemia, and minimal-change nephritic syndrome, secondary glomerulonephritis, vasculitis, pyelonephritis, nephrocalcinosis, nephrolithiasis, chronic or acute interstitial nephritis, hypertensive or large vessel diseases (including renal artery stenosis or occlusion and cholesterol

emboli or renal emboli), renal or urological neoplasms, multiple myelomas, lymphomas, light chain neuropathy, amyloidosis, asthma and other chronic airway diseases such as bronchitis and emphysema, insulin dependent diabetes mellitus, and Crohn's disease. The methods of the invention can also be used for inhibiting or neutralizing an effector T cell response and for treating conditions requiring immunosuppression, such as graft versus host disease and graft rejection, chronic inflammatory diseases, in particular, to lessen joint pain, swelling, anemia, and septic shock.

[0048] In the methods of the invention, the antagonist(s) is(are) administered as the sole active compound(s) or in combination with other compound(s) or composition(s). Unless otherwise indicated, the dose of antagonists administered is approximately 1 µg/kg and 250 mg/kg, depending on the severity of the symptoms and the progression of the disease. Most commonly, antibodies or immunoglobulin fusion proteins are administered in an outpatient setting by weekly administration of about 0.1-10 mg/kg doses by slow intravenous (IV) infusion. The appropriate therapeutically effective dose of an antagonist is selected by a treating clinician and would range approximately from 1 µg/kg to 100 mg/kg, 1 µg/kg to 50 mg/kg, 1 µg/kg to 20 mg/kg, 1 µg/kg to 10 mg/kg, 1 µg/kg to 1 mg/kg, 10 µg/kg to 1 mg/kg, 10 µg/kg to 100 µg/kg, 100 µg to 1 mg/kg, or 500 µg/kg to 5 mg/kg. Alternatively, specific dosages indicated in the Examples or for similar drugs in the Physicians' Desk Reference (PDR) 2003, 57th ed., Medical Economics Company, 2002, may be used.

Compositions

[0049] BAFF antagonists used in the methods of the present invention, include (but are not limited to) antibodies directed against BAFF, antibodies directed against one or more isoforms of at least one BAFF receptor, and soluble forms of BAFF receptors.

[0050] BAFF receptors include BAFFR, BCMA, and TACI. In some embodiments, the BAFF antagonist is BAFF-specific (e.g., BAFFR), while in certain other embodiments the BAFF antagonist may also bind TNF family ligands other than BAFF (e.g., BCMA and TACI which also bind to APRIL). In some embodiments, the BAFF antagonist is an antibody that blocks BAFF binding to its receptor. Antibodies directed to BAFF and to BAFF receptors have been previously described. Producing such antibodies is well within the skill of a person skilled in the art (see, e.g., Antibody Engineering, ed. Borrebaeck, 2nd ed., Oxford University Press, 1995). Examples of antibodies for use in the methods of the invention include those described in PCT Publication WO 99/12964 and United States Patent Application No. 09/911,777) and the anti-BAFF antibody LymphoStat-B™ (Human Genome Sciences, Rockville, MD). In further embodiments, the antibody of the invention may specifically bind, besides BAFF or BAFFR, another protein that is substantially identical to BAFF or BAFFR, respectively. In yet further embodiments, antibodies are directed against BCMA and/or TACI. Also contemplated for use in humans are humanized forms and derivatives of nonhuman antibodies derived from any vertebrate species.

[0051] Other examples of antibodies for use in the methods of the invention include mouse monoclonal antibodies produced by hybridoma clone # 2.1, deposited as ATCC No. PTA-3689, or by clone # 9.1, deposited as ATCC No. PTA-3688, or humanized chimeric, or fully human derivatives thereof.

[0052] Soluble forms of BAFF receptor fusion proteins may comprise a BAFF-binding domain of BAFFR, BCMA, and/or TACI. A BAFF-binding domain is located within the extracellular domains (ECD), i.e., the portion of the protein normally present on the exterior of a cell expressing the protein. In some embodiments, the soluble BAFFR is a disulfide-linked peptide having the sequence CHWDLRLHWVC (SEQ ID NO:5) (Kayagaki et al. (2002) Immunity, 10:515-524), or a polypeptide comprising this sequence. In yet other embodiments, the soluble BAFFR is a polypeptide comprising amino acids 27 to 32 or 18 to 43 of SEQ ID NO:1.

[0053] In certain embodiments, a soluble form a BAFF receptor comprises a BAFF-binding domain of a BAFF receptor fused to a constant region of an immunoglobulin, i.e., as in BAFFR-Fc. In some embodiments, BAFFR-Ig comprises residues 3 to 73 of SEQ ID NO:1 fused to the Fc portion of IgG. In illustrative embodiments, BAFFR-Fc comprises SEQ ID NO:2 (human) or SEQ ID NO:4 (murine). In some embodiments, BAFFR is a human BAFFR having a C-terminal deletion starting from amino acid 51 of SEQ ID NO:1, which results in an altered O-linked glycosylation pattern (e.g., Δ BAFFR described in United States Patent Application No. 60/458,707). In some embodiments, soluble BAFFR comprises Δ BAFFR which lacks at least

the sequence of SEQ ID NO:6 (corresponding to amino acids 51-57 of SEQ ID NO:1).

[0054] The BAFF-binding domain of BAFFR comprises amino acids (aa) 8 to aa 50, aa 13 to aa 50, or aa 13 to aa 43, or aa 18 to aa 43 of SEQ ID NO:1. In certain embodiments, the BAFF-binding domain is identical or substantially identical to aa 2 to aa 63 of SEQ ID NO:1 or to aa 2 to aa 62 of SEQ ID NO:3, including sequences that have been truncated or mutated so long as such sequences retain the ability to bind BAFF. In illustrative embodiments, BAFFR is a murine sequence as set out from aa 2 to aa 66 of SEQ ID NO:3. In other embodiments, BAFFR comprises at least 20, 25, 30, 35, 40, 45, or 50 contiguous amino acids of SEQ ID NO:1.

[0055] In certain embodiments, the constant region of an immunoglobulin comprises any one of CH1, CH2, or CH3 constant regions, or the entire Fc portion (that includes CH2, or CH3), with or without a hinge region. In more embodiments, the second amino acid sequence is derived from the Fc portion of an IgG. In related embodiments, the Fc portion is derived from IgG1, IgG4, or another IgG isotype. In illustrative embodiments, the contract region of an immunoglobulin comprises a sequence from aa 95 to aa 321 of SEQ ID NO:3, or aa 88 to aa 316 of SEQ ID NO:4. The second amino acid sequence may comprise the Fc portion of human IgG1, wherein the Fc is modified to minimize the effector function. Such modifications include changing specific amino acid residues that might alter an effector function such as Fc receptor binding (Lund et al. (1991) J. Immun., 147:2657-2662 and Morgan et al. (1995) Immunology, 86:319-324), or

changing the species from which the constant region is derived.

Immunoglobulins may have mutations in the CH2 region of the heavy chain that reduce effector function, i.e., Fc receptor binding and complement activation. For example, immunoglobulins may have mutations such as those described in U.S. Patent Nos. 5,624,821 and 5,648,260. In the IgG1 or IgG2 heavy chain, for example, such mutations may be made at amino acid residues corresponding to amino acids 234 and 237 in the full-length sequence of IgG1 or IgG2. Antibodies and immunoglobulin-receptor fusion proteins may also have mutations that stabilize the disulfide bond between the two heavy chains of an immunoglobulin, such as mutations in the hinge region of IgG4, as disclosed in Angal et al. (1993) *Mol. Immunol.*, 30:105-108.

[0056] In certain embodiments, a BAFF-binding domain is fused at the C-terminus or the N-terminus, with or without a linker sequence, to the C-terminus or the N-terminus of the constant region of an immunoglobulin. The exact length and sequence of the linker and its orientation relative to the linked sequences may vary. The linker may, for example, comprise one or more Gly-Ser. The linker may be 2, 10, 20, 30, or more amino acid long and is selected based on properties desired such as solubility, length and steric separation, immunogenicity, etc. It will be understood by one of ordinary skill in the art that certain amino acids in a sequence of any protein may be substituted for other amino acids without adversely affecting the activity of the protein. It is thus contemplated that various changes may be made in the amino acid sequences of BAFF receptor of the invention, or DNA sequences

encoding therefore, as provided, without appreciable loss of their biological activity or utility.

[0057] The use of derivatives and analogs of BAFF receptors are also within the scope of the present invention. The derivatives or analogs should be functionally active, i.e., capable of exhibiting one or more activities associated with a ligand-binding domain of the wild-type BAFFR. Derivatives or analogs that retain this binding ability, or inhibit biological activity of BAFF can be produced and tested by procedures known in the art and/or as described in the Examples. Methods of producing such derivatives and analogs include recombinant and synthetic methods (see, e.g., Maniatis (1990) *Molecular Cloning; A Laboratory Manual*, 2nd ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, and Bodansky et al. (1995) *The Practice of Peptide Synthesis*, 2nd ed., Springer Verlag, Berlin, Germany).

[0058] The following examples provide illustrative embodiments of the invention. While the representative procedures are performed in mice, a skilled artisan recognizes that they can be successfully performed within parameters clinically feasible in human subjects. The skilled artisan will recognize the numerous modifications and variations that may be performed without altering the spirit or scope of the present invention. Such modifications and variations are encompassed within the scope of the invention. The examples do not in any way limit the invention.

EXAMPLES

[0059] The following describes materials and methods used in the representative procedures and experiments described in the subsequent Examples.

Mice

[0060] Female (SWR xNZB)F1 (SNF1) mice were bred and maintained as previously described in, e.g., Gavalchin et al. (1987) J. Immunol., 138:138-148; Datta et al. 1989 Clin. Immunol. Immunopathol., 51:141-56.

Protein reagents

[0061] An expression vector containing murine BAFFR-mulG1 (BAFFR-Fc) was constructed by ligating a Not1 + Aat2 fragment containing a signal sequence from a murine Ig-k gene, an Aat2 + Sal1 fragment containing the sequence encoding aa 2 to aa 66 of murine BAFFR (Accession No. AF373847) and a Sal+Not1 fragment containing the sequence encoding aa 226 to aa 478 of murine IgG1 (Kabat system of numbering) into the Not1 site of a modified version (without the EBNA-1 gene) of pCEP4 (Invitrogen, Carlsbad, CA), called CH269. The vector was transfected into 293 cells containing the EBNA-1 gene using Lipofectamine™ according to the manufacturer's protocol (Invitrogen). The transfection was maintained in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal calf serum (FCS), 2 mM glutamine, 100 U/ml penicillin, 100 µg/ml streptomycin and 250 µg/ml G418. Medium was harvested every 4-7 days for

several weeks. The conditioned medium was diluted with three volumes of high salt and high pH buffer (1.5 M glycine pH 8.9, 3 M NaCl) to increase the affinity of mBAFFR-mIgG for protein A. The BAFFR-Fc protein was purified by affinity chromatography (protein A) followed by size exclusion chromatography. Mouse IgG1 (mIgG1), produced by the MOPC21 hybridoma was purified in a similar fashion and was used as a negative control.

Treatment protocol

[0062] Twenty 23 week-old female SNF1 mice with established nephritis (proteinuria of 30-100 mg/dL) were divided into two cohorts of ten mice/group. One cohort received 200 µg of mouse BAFFR-Fc and the other received 200 µg of mIgG1, 2 times per week for 4 consecutive weeks, and monitored thereafter for progression of disease. Mice that became moribund were euthanized, and tissues and blood samples were collected for analysis prior to sacrifice. Blood was also collected via the retro-orbital sinus at regular intervals for obtaining serum for autoantibody determination. At termination of the study, kidneys, hearts, and mesenteric lymph nodes (MLN) were placed in 10% neutral buffered saline and embedded into paraffin blocks for histologic analysis. The spleens were collected and used for flow cytometry.

Flow cytometry

[0063] Single cell suspensions were made of splenocytes by mechanical disruption. Erythrocytes were lysed in an ammonium chloride solution, and cells were then washed 3 times, filtered through a 100-micron filter, and counted using a hemocytometer. Splenocytes were stained with a

fluorochrome-conjugated anti-B220 mAb to detect B lymphocytes as described in Thompson et al. (2001) Science, 293:2108-2111.

Histology

[0064] Paraffin-embedded mesenteric lymph nodes (MLN) and kidney sections were assessed lymphocyte infiltration using rat anti-B220 mAb for B cells and rat anti-CD3 mAb for T cells, followed by biotinylated rabbit anti-rat and avidin-biotin-HRP solution, and visualized using the substrate DAB (Vector Laboratories, Burlingame, CA). Kidney fibrosis was assessed by staining kidneys with Mason's trichrome stain and biotin-labeled anti- α smooth muscle actin followed by incubation with streptavidin-HRP and visualized with DAB substrate. Slides were counterstained with Mayer's hematoxylin. Heart inflammation was assessed by examination of H&E-stained heart tissues.

Assessment of renal and cardiac disease

[0065] The urine of each mouse was monitored weekly with Albustix™ (Bayer Corp., Research Triangle Park, NC) to measure proteinuria. H&E-stained kidney sections were used for histologic examination and scored for: glomerular hypercellularity, enlargement, crescents, mesangial thickening, loops, fibrinoid necrosis and hyaline; interstitial sclerosis, infiltrate and vasculitis; and tubule vasculitis, atrophy and casts. Heart tissues were examined for vascular and cardiac inflammation and cardiac vacuolation. The grades of 0-4+ were given based on percent involvement of the structure being examined, wherein 0=none and 4+ is 100% involvement.

ELISA

[0066] The ELISA assay used to detect serum anti-ssDNA antibody was performed as described in Kalled et al. (1998) J. Immunol., 160:2158-2165.

Example 1: Short-term BAFFR-Fc administration increases survival

[0067] As shown in Table 1, a short-course of BAFFR-Fc treatment markedly enhanced survival when compared to mIgG control-treated mice. At age 49 weeks, all BAFFR-Fc-treated mice were alive, while only 30% of control mice remained alive.

Table 1

Age (weeks)	Percent survival	
	Treatment	
	BAFFR-Fc	mIgG
23	100	100
29	100	100
30	100	90
31	100	90
32	100	80
33	100	70
34	100	30
49	100	30

Example 2: Short-term BAFFR-Fc administration reduces progression of nephritis

[0068] Renal function was assessed by proteinuria determination at regular intervals. As shown in Table 2, progression of disease to severe nephritis (proteinuria ≥ 300 mg/dL) was significantly reduced in BAFFR-Fc-treated mice when compared to mIgG-treated control mice. By

age 49 weeks, all control mice developed severe nephritis, while no BAFFR-Fc-treated animal had severe nephritis at that age. In a separate experiment, SNF1 mice were treated with human IgG or with human TACI-Fc (a receptor-Fc fusion protein that binds to both BAFF and APRIL) at 200 µg twice per week for four weeks. Although TACI-Fc administration somewhat reduced the incidence of severe nephritis initially, eventually all TACI-Fc-treated mice developed severe nephritis similarly to controls (Table 2).

Table 2

Age (wks)	Percent incidence of severe nephritis			
	Treatment			
	BAFFR-Fc	mIgG	Human TACI-Fc	Human IgG
23	0	0	0	0
27	0	30	34	60
30	0	70	60	80
36	0	90	100	100
49	0	100	100	100

[0069] Renal disease was further assessed by an histologic approach. H&E stained kidney sections were scored for renal disease by combining the scores of the individual disease parameters described in Materials and Methods. As seen in Table 3, BAFFR-Fc-treated mice had significantly reduced cumulative disease scores when compared to mIgG-treated or untreated controls, and the scores of BAFFR-Fc-treated mice were closer to that of young SNF1 mice, prior to disease onset.

Table 3

Age (weeks)	Cumulative kidney disease score (mean \pm SD)		
	BAFFR-Fc	untreated	mIgG
9 49-51	6.3 \pm 2.5 (n=10)	1 \pm 0 (n=3) ¹ 24.3 \pm 8.6 (n=4)	23.9 \pm 8.6 (n=7)

¹ n indicates the number of mice used in analysis.

[0070] In SLE-nephritis, renal fibrosis often occurs and may be mediated by secretion of extracellular matrix (ECM) proteins, α -smooth muscle actin (ASMA) and collagen, by fibroblasts and mesangial cells. ECM production was significantly ($p < 0.05$, Student's t test) diminished in mice treated with BAFFR-Fc as compared to untreated and mIgG-treated SNF1 mice, as observed by reduced ASMA (Table 4) and collagen (Table 5) deposition in the kidneys. Young, 9 week-old SNF1 mice were used as pre-disease controls.

Table 4

Age (weeks)	Percent glomeruli exhibiting collagen deposition ¹ (mean \pm SD)		
	BAFFR-Fc	untreated	mIgG
9 49-51	3.3 \pm 8.8 (n=10)	0 (n=3) 48.2 \pm 36.2 (n=4)	68.8 \pm 33.2 (n=7)

¹ 70-111 glomeruli were examined for each mouse.

Table 5

Age (weeks)	Percent glomeruli exhibiting ASMA production ¹ (mean \pm SD)		
	BAFFR-Fc	untreated	mIgG
9 49-51	8.5 \pm 10.9 (n=10)	0 (n=3) 57.5 \pm 29.5 (n=4)	68.5 \pm 32.1 (n=7)

¹ 70-111 glomeruli were examined for each mouse.

[0071] Healthy kidneys do not harbor lymphoid clusters. However, accompanying disease in this model of SLE-nephritis, as well as in human disease, is infiltration of leukocytes into the kidney, including B and T cells, forming follicular-like structures. Therefore, kidney sections were examined for the presence of T and B cell infiltrates. In untreated (Fig. 1B) and mIgG-treated (Fig. 1D) mice, large areas of T and B cell infiltrates that mimic white pulp areas of secondary lymphoid tissues were observed throughout the kidneys. In contrast, in kidneys of mice that received short-term BAFFR-Fc treatment (Fig. 1C), infiltration of B cells, as well as T cells, was markedly reduced (Fig. 1). Few or no B or T cells were observed in healthy, 9 week-old (pre-disease) SNF1 mice (Fig. 1A).

Example 3: Short-term BAFFR-Fc administration inhibits cardiac inflammation

[0072] H&E-stained paraffin sections of hearts were examined for vascular and cardiac inflammation, and cardiac vacuolation. As seen in Table 6, SNF1 mice that received BAFFR-Fc had an overall markedly reduced cardiac score when compared to mIgG and untreated control mice.

Table 6

Age (weeks)	Cardiac score (mean \pm SD)		
	BAFFR-Fc	untreated	mIgG
9		0 (n=3) ¹	
49-51	1.2 \pm 0.4 (n=10)	2.5 \pm 1.1 (n=4)	4.7 \pm 1.9 (n=3)

¹ n indicates the number of mice used in the analysis.

Example 4: Short-term BAFFR-Fc administration prevents B cell hyperplasia

[0073] Based on a study of BAFF blockade in normal BALB/c mice with BAFFR-Fc, 100 µg once a week for 4 consecutive weeks, peripheral B cell numbers are known to be fully restored within about 9 weeks after the last dose of BAFFR-Fc (data not shown). The number of splenic B cells in the SNF1 mice was determined 26-28 weeks after the last dose of BAFFR-Fc or mIgG. As seen in Table 7, SNF1 mice that received a short course of BAFFR-Fc treatment had a significantly reduced ($p < 0.05$, Student's t test) splenic B cell number than untreated or mIgG-treated control mice. With time, control mice developed severe splenic B cell hyperplasia. In contrast, BAFFR-Fc-treated mice exhibited a long-term benefit wherein at the end of the study, splenic B cell counts were between that of pre-disease, 9 week-old SNF1 mice, and 20 week-old SNF1 mice that have begun to experience B cell expansion.

Table 7

Age (weeks)	Number of splenic B cells ($\times 10^6$)		
	BAFFR-Fc	untreated	mIgG
9		34.3 \pm 9 (n=3)	
20		123 (n=1)	
49-51	77.4 \pm 41.7 (n=10)	197.4 \pm 62 (n=4)	141 \pm 70.6 (n=3)

[0074] In addition, immunohistochemical analysis of the B and T cell organization in MLN demonstrated that untreated (Fig. 2B) and mIgG-treated (Fig. 2D) mice had extensive B cell expansion, resulting in lymphadenopathy. In contrast, BAFFR-Fc-treated mice (Fig. 2C), did not exhibit B cell

hyperplasia and looked similar to young SNF1 mice prior to disease onset (Fig. 2A).

Example 5: Short-term BAFFR-Fc administration inhibits increasing production of autoantibody

[0075] Sera obtained from SNF1 mice at regular intervals were analyzed for circulating anti-ssDNA antibody using an ELISA format. When examining the change of anti-ssDNA levels with time, from the start of treatment to age 37 weeks, there is a significant change (increase) in anti-ssDNA in the mIgG-treated mice ($p < 0.05$ using the Student-Newman-Keuls method), however, there is no significant change in autoantibody levels in mice that received BAFFR-Fc (Table 8). This indicates that BAFF blockade with BAFFR-Fc inhibits autoantibody production, which may contribute to decreased pathology in BAFFR-Fc-treated mice. Notably, autoantibody levels remained decreased compared with controls 10 weeks (age 37 weeks) after the last dose of BAFFR-Fc had been administered.

Table 8

Age (weeks)	Anti-ssDNA ($\mu\text{g/ml}$)	
	Treatment	
	BAFFR-Fc (n=10)	mIgG (n=10)
23	0.1 ¹	0.15
29	0.4	1.1
37	0.7	24.3

¹ Values reflect geometric means.

Example 6: Short-term BAFFR-Fc administration reduces percentage of IgM⁺IgD⁺ B cells

[0076] At the end of the study, BAFFR-Fc-treated and mIgG-treated mice had a similar frequency of total B cells in the blood, based on staining for

B220⁺ B cells. However, when specific B cell subsets were examined, BAFFR-Fc-treated mice exhibited a statistically significant reduction ($p < 0.01$, Student's t test) in the percent of IgM⁺IgD⁺ B cells (Table 9). The general reconstitution of peripheral B cells, yet the selective, marked reduction in IgM⁺IgD⁺ B cells and long-term efficacy in BAFFR-Fc-treated mice suggests that BAFFR-Fc causes a long-term reduction in these presumably pathogenic B cells.

Table 9

	Percent blood B cells (mean \pm SD)	
	BAFFR-Fc ¹	mIgG ¹
IgM ⁺ IgD ⁺ B cells	8.7 \pm 5.0	44.9 \pm 7.3
Total B220 ⁺ B cells	47.3 \pm 9.3	49.6 \pm 8.6

¹Mice were 49-51 weeks of age at the time of analysis.

[0077] The specification is most thoroughly understood in light of the teachings of the references cited within the specification. The embodiments within the specification provide an illustration of embodiments of the invention and should not be construed to limit the scope of the invention. The skilled artisan readily recognizes that many other embodiments are encompassed by the invention. All publications and patents and sequences cited in this disclosure are incorporated by reference in their entirety. To the extent the material incorporated by reference contradicts or is inconsistent with the present specification, the present specification will supercede any such material. The citation of any references herein is not an admission that such references are prior art to the present invention.

[0078] The following applies unless otherwise indicated: all numbers expressing quantities of ingredients, cell culture, treatment conditions, and so forth used in the specification, including claims, are to be understood as being modified in all instances by the term "about"; the term "at least" preceding a series of elements is to be understood to refer to every element in the series. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

CLAIMS

1. A method of treating a patient having an immunologic disorder, comprising:
 - (a) administering to the patient a therapeutically effective amount of a BAFF (B cell activating factor belonging to the TNF family) antagonist at least once or at one or more intervals of less than N weeks;
 - (b) temporarily discontinuing the administration of step (a) for N weeks or longer; and
 - (c) repeating steps (a) and (b) at least once;wherein N is 8, 9, 10, 11, or 12.
2. The method of claim 1, wherein the administration of step (a) comprises an interval of 1, 2, 3, 4, 5, 6, or 7 weeks.
3. The method of claim 1, wherein the BAFF antagonist is administered in step (a) 2, 3, 4, 5, 6, or 7 times a week.
4. The method of claim 1, wherein the administration is discontinued in step (b) for 12, 18, 24, 30, 36, 42, 48 weeks or longer.
5. The method of claim 1, wherein at the beginning of the treatment the patient has one or more of:
 - (i) proteinuria of 1 g per a 24-hour period or higher;
 - (ii) serum creatinine levels of about 1 mg/dl or higher;
 - (iii) creatinine clearance levels of 97 ml/min or lower;
 - (iv) blood urea of 20 mg/dl or higher;
 - (v) abnormal titer of autoantibodies in the serum; and
 - (vi) peripheral blood B cell count of 700 cells/ μ l.

6. The method of claim 5, wherein the patient is human.
7. The method of claim 1, wherein the therapeutically effective amount of the BAFF antagonist is sufficient to inhibit autoantibody titer.
8. The method of claim 1, wherein the therapeutically effective amount of the BAFF antagonist is sufficient to reduce B cell hyperplasia.
9. The method of claim 1, wherein the therapeutically effective amount of the BAFF antagonist is sufficient to reduce cardiac inflammation.
10. The method of claim 1, wherein the therapeutically effective amount of the BAFF antagonist is sufficient to improve renal function.
11. The method of claim 10, wherein the renal function is one or more of: pressure filtration, selective reabsorption, tubular secretion, and systemic blood pressure regulation.
12. The method of claim 1, wherein the therapeutically effective amount of the BAFF antagonist is sufficient to reduce progression of renal fibrosis.
13. The method of claim 1, wherein the therapeutically effective amount of the BAFF antagonist is sufficient to reduce lymphocyte infiltration in the kidneys.
14. The method of claim 1, wherein the therapeutically effective amount of the BAFF antagonist is sufficient to reduce lymphadenopathy.
15. The method of claim 1, wherein the immunologic disorder is an autoimmune disorder.
16. The method of claim 15, wherein the autoimmune disorder is systemic lupus erythematosus.

17. The method of any one of claims 1-16, wherein the medicament is LymphoStat-B™.

18. The method of any one of claims 1-16, wherein the BAFF antagonist is BAFF-specific.

19. The method of claim 18, wherein the BAFF antagonist is selected from the group consisting of a soluble BAFF receptor, an anti-BAFF antibody and an anti-BAFFR antibody.

20. The method of claim 19, wherein the BAFF receptor is selected from the group consisting of BAFFR, BCMA (B cell maturation antigen) and TACI (transmembrane activator and cyclophilin ligand interactor).

21. The method of claim 20, wherein the soluble BAFFR comprises the peptide of SEQ ID NO:5.

22. The method of claim 19, wherein the soluble BAFF receptor comprises a BAFF-binding domain of BAFFR.

23. The method of claim 20, wherein the soluble BAFFR is human.

24. The method of claim 20, wherein the soluble BAFFR lacks the sequence of SEQ ID NO:6.

25. The method of claim 22, wherein the BAFF-binding domain of BAFFR has an amino acid sequence as set out:

- (a) from amino acid 27 to amino acid 32 of SEQ ID NO:1;
- (b) from amino acid 18 to amino acid 43 of SEQ ID NO:1;
- (c) from amino acid 13 to amino acid 50 of SEQ ID NO:1;
- (d) from amino acid 3 to amino acid 73 of SEQ ID NO:1; or
- (e) amino acid 2 to amino acid 62 of SEQ ID NO:3.

26. The method of claim 22, wherein the BAFF-binding domain of BAFFR is fused to a constant region of an immunoglobulin.
27. The method of claim 26, wherein the immunoglobulin is IgG₁ or IgG₄.
28. The method of claim 26, wherein the constant region of an immunoglobulin comprises an Fc portion.
29. The method of claim 28, wherein the BAFFR-Fc comprises (a) an amino acid sequence as set out in SEQ ID NO:2 or (b) an amino acid sequence as set out in SEQ ID NO:4.
30. A method of treating a patient having an autoimmune disorder, comprising:
- (a) administering to the patient a therapeutically effective amount of a BAFF-specific antagonist at least once or at one or more intervals of less than *N* weeks;
 - (b) temporarily discontinuing the administration of step (a) for *N* weeks or longer; and
 - (c) repeating steps (a) and (b) at least once;
- thereby treating the autoimmune disorder, and wherein *N* is 8, 9, 10, 11, or 12.
31. A method of reducing autoantibody titer in a patient, comprising:
- (a) administering to the patient a therapeutically effective amount of a BAFF-specific antagonist at least once or at one or more intervals of less than *N* weeks;

(b) temporarily discontinuing the administration of step (a) for N weeks or longer; and

(c) repeating steps (a) and (b) at least once;

thereby reducing autoantibody titer, and wherein N is 8, 9, 10, 11, or

12.

32. A method of inhibiting generation of pathogenic B cells in a patient, comprising:

(a) administering to the patient a therapeutically effective amount of a BAFF-specific antagonist at least once or at one or more intervals of less than N weeks;

(b) temporarily discontinuing the administration of step (a) for N weeks or longer; and

(c) repeating steps (a) and (b) at least once;

thereby inhibiting generation of pathogenic B cells, and wherein N is 8, 9, 10, 11, or 12.

33. The method of claim 32, wherein the pathogenic B cells are IgM⁺ IgD⁺.

34. The method of any one of claims 30-33, wherein the BAFF-specific antagonist is a soluble form of BAFFR.

35. The method of any one of claims 30-33, wherein the BAFF-specific antagonist is an anti-BAFF-antibody.

36. Use of a BAFF antagonist for preparation of a medicament for treatment of an immunologic disorder, wherein the treatment regimen comprises:

(a) administering a therapeutically effective amount of a BAFF (B cell activating factor belonging to the TNF family) antagonist at least once or at one or more intervals of less than N weeks;

(b) temporarily discontinuing the administration of step (a) for N weeks or longer; and

(c) repeating steps (a) and (b) at least once;

wherein N is 8, 9, 10, 11, or 12.

37. The use of claim 36, wherein the administration of step (a) comprises an interval of 1, 2, 3, 4, 5, 6, or 7 weeks.

38. The use of claim 36, wherein the BAFF antagonist is administered in step (a) 2, 3, 4, 5, 6, or 7 times a week.

39. The use of claim 36, wherein the administration is discontinued in step (b) for 12, 18, 24, 30, 36, 42, 48 weeks or longer.

40. The use of claim 36, wherein at the beginning of the treatment the patient has one or more of:

- (i) proteinuria of 1 g per a 24-hour period or higher;
- (ii) serum creatinine levels of about 1 mg/dl or higher;
- (iii) creatinine clearance levels of 97 ml/min or lower;
- (iv) blood urea of 20 mg/dl or higher;
- (v) abnormal titer of autoantibodies in the serum; and
- (vi) peripheral blood B cell count of 700 cells/ μ l.

41. The use of claim 40, wherein the patient is human.

42. The use of claim 36, wherein the therapeutically effective amount of the BAFF antagonist is sufficient to inhibit autoantibody titer.

43. The use of claim 36, wherein the therapeutically effective amount of the BAFF antagonist is sufficient to reduce B cell hyperplasia.

44. The use of claim 36, wherein the therapeutically effective amount of the BAFF antagonist is sufficient to reduce cardiac inflammation.

45. The use of claim 36, wherein the therapeutically effective amount of the BAFF antagonist is sufficient to improve renal function.

46. The use of claim 45, wherein the renal function is one or more of: pressure filtration, selective reabsorption, tubular secretion, and systemic blood pressure regulation.

47. The use of claim 36, wherein the therapeutically effective amount of the BAFF antagonist is sufficient to reduce progression of renal fibrosis.

48. The use of claim 36, wherein the therapeutically effective amount of the BAFF antagonist is sufficient to reduce lymphocyte infiltration in the kidneys.

49. The use of claim 36, wherein the therapeutically effective amount of the BAFF antagonist is sufficient to reduce lymphadenopathy.

50. The use of claim 36, wherein the immunologic disorder is an autoimmune disorder.

51. The use of claim 50, wherein the autoimmune disorder is systemic lupus erythematosus.

52. The use of any one of claims 36-51, wherein the medicament is LymphoStat-B™.

53. The use of any one of claims 36-51, wherein the BAFF antagonist is BAFF-specific.

54. The use of claim 53, wherein the BAFF antagonist is selected from the group consisting of a soluble BAFF receptor, an anti-BAFF antibody, and an anti-BAFFR antibody.

55. The use of claim 54, wherein the soluble BAFF receptor is selected from the group consisting of BAFFR, BCMA (B cell maturation antigen) and TACI (transmembrane activator and cyclophilin ligand interactor).

56. The use of claim 55, wherein the BAFFR comprises the peptide of SEQ ID NO:5.

57. The use of claim 54, wherein the soluble BAFF receptor comprises a BAFF-binding domain of BAFFR.

58. The use of claim 55, wherein the BAFFR is human.

59. The use of claim 55, wherein the BAFFR lacks the sequence of SEQ ID NO:6.

60. The use of claim 57, wherein the BAFF-binding domain of BAFFR has an amino acid sequence as set out:

- (a) from amino acid 27 to amino acid 32 of SEQ ID NO:1;
- (b) from amino acid 18 to amino acid 43 of SEQ ID NO:1;
- (c) from amino acid 13 to amino acid 50 of SEQ ID NO:1;
- (d) from amino acid 3 to amino acid 73 of SEQ ID NO:1; or
- (e) amino acid 2 to amino acid 62 of SEQ ID NO:3.

61. The use of claim 57, wherein the BAFF-binding domain of BAFFR is fused to a constant region of an immunoglobulin.
62. The use of claim 61, wherein the immunoglobulin is IgG₁ or IgG₄.
63. The use of claim 61, wherein the constant region of an immunoglobulin comprises an Fc portion.
64. The use of claim 63, wherein the BAFFR-Fc comprises (a) an amino acid sequence as set out in SEQ ID NO:2 or (b) an amino acid sequence as set out in SEQ ID NO:4.
65. Use of a BAFF-specific antagonist for preparation of a medicament for treatment of an autoimmune disorder, wherein the treatment regimen comprises:
- (a) administering to the patient a therapeutically effective amount of a BAFF-specific antagonist at least once or at one or more intervals of less than *N* weeks;
 - (b) temporarily discontinuing the administration of step (a) for *N* weeks or longer; and
 - (c) repeating steps (a) and (b) at least once;
- thereby treating an autoimmune disorder, and wherein *N* is 8, 9, 10, 11, or 12.
66. Use of a BAFF-specific antagonist for preparation of a medicament for reducing autoantibody titer, wherein the treatment regimen comprises:

- (a) administering to the patient a therapeutically effective amount of a BAFF-specific antagonist at least once or at one or more intervals of less than N weeks;
 - (b) temporarily discontinuing the administration of step (a) for N weeks or longer; and
 - (c) repeating steps (a) and (b) at least once;
- thereby reducing autoantibody titer, and wherein N is 8, 9, 10, 11, or 12.

67. Use of a BAFF-specific antagonist for preparation of a medicament for inhibiting generation of pathogenic B cells, wherein the treatment comprises:

- (a) administering to a patient a therapeutically effective amount of a BAFF-specific antagonist at least once or at one or more intervals of less than N weeks;
 - (b) temporarily discontinuing the administration of step (a) for N weeks or longer; and
 - (c) repeating steps (a) and (b) at least once;
- wherein N is 8, 9, 10, 11, or 12.

68. The use of claim 67; wherein the pathogenic B cells are IgM⁺ IgD⁺.

69. The use of any one of claims 65-68, wherein the BAFF-specific antagonist is a soluble form of BAFFR.

70. The use of any one of claims 65-68, wherein the BAFF-specific antagonist is an anti-BAFF-antibody.



Fig. 1B



Fig. 1D



Fig. 1A

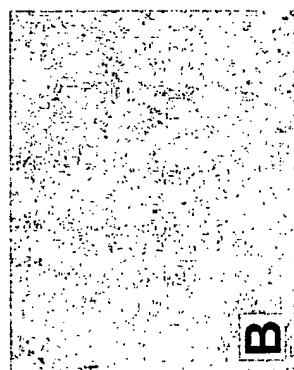
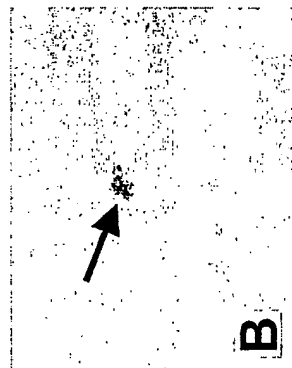


Fig. 1C



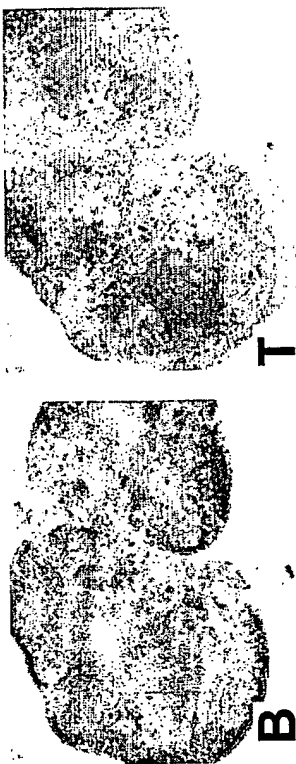


Fig. 2B

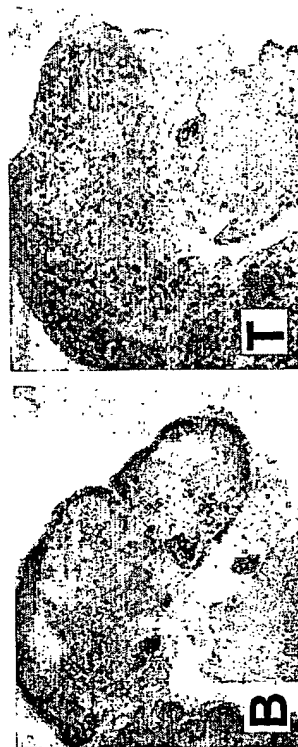


Fig. 2D

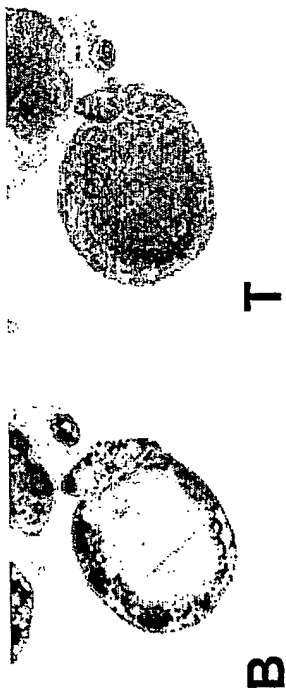


Fig. 2A

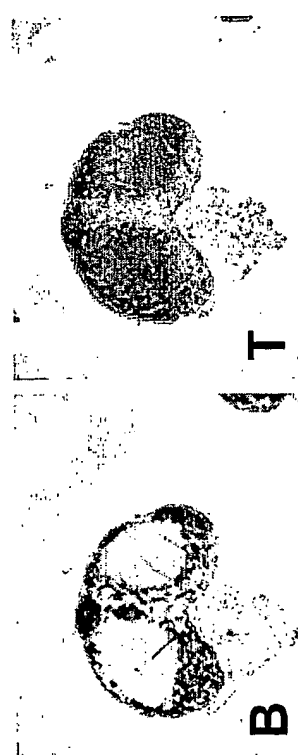


Fig. 2C

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<120> Therapeutic regimens for BAFF antagonists

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INTERNATIONAL SEARCH REPORT

Interr - pplication No
PCT/US2004/034514

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K38/19 A61K39/395 A61P37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, EMBL, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KAYAGAKI NOBUHIKO ET AL: "BAFF/BLyS receptor 3 binds the B cell survival factor BAFF ligand through a discrete surface loop and promotes processing of NF-kappaB2" IMMUNITY, vol. 10, no. 4, October 2002 (2002-10), pages 515-524, XP002321480 ISSN: 1074-7613 the whole document ----- -/--	1-16, 18-28, 30-33, 36-51, 53-63, 65-68

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

23 March 2005

Date of mailing of the international search report

06/04/2005

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
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Authorized officer

Mateo Rosell, A.M.

INTERNATIONAL SEARCH REPORT

Intern

pplication No

PCT/US2004/034514

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GROSS J A ET AL: "TACI and BCMA are receptors for a TNF homologue implicated in B-cell autoimmune disease" NATURE, MACMILLAN JOURNALS LTD. LONDON, GB, vol. 404, 27 April 2000 (2000-04-27), pages 995-999, XP002140939 ISSN: 0028-0836 abstract page 998, left-hand column, paragraph 2 - right-hand column, paragraph 1 -----	1-16, 18-28, 30-33, 36-51, 53-63, 65-68
Y	PELLETIER MARC ET AL: "Comparison of soluble decoy IgG fusion proteins of BAFF-R and BCMA as antagonists for BAFF." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 278, no. 35, 29 August 2003 (2003-08-29), pages 33127-33133, XP002321479 ISSN: 0021-9258 the whole document -----	1,20-22, 26-35, 64-70
Y	WO 02/24909 A (BIOGEN, INC; AMBROSE, CHRISTINE, M; THOMPSON, JEFFREY, S) 28 March 2002 (2002-03-28) abstract page 7, paragraphs 2,3; figure 9; sequence 12 page 75, paragraphs 3,4 -----	1-16, 18-51, 53-70
P,X	STOHL W: "A therapeutic role for BLyS antagonists" LUPUS, vol. 13, no. 5, 2004, pages 317-322, XP008044502 ISSN: 0961-2033 the whole document -----	1-70

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2004/034514

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-35 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern

Application No

PCT/US2004/034514

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0224909	A	28-03-2002	AU 8885801 A	02-04-2002
			BG 107621 A	30-01-2004
			BR 0113921 A	14-12-2004
			CA 2422622 A1	28-03-2002
			EE 200300107 A	15-02-2005
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			NO 20031248 A	16-05-2003
			SK 4712003 A3	07-10-2003
			WO 0224909 A2	28-03-2002
			ZA 200301903 A	25-06-2004

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